REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

The specification has been amended to correct minor typographical errors at pages 24, 25 and 37. The error on page 37 was an error made during preparation of the English translation of the PCT Japanese language application, which does not contain the line describing cellulose content. A copy of the corresponding page of the PCT publication and its English translation are enclosed for the Examiner's information.

Claims 1, 6, 11 and 16 are withdrawn.

Claims 2-5, 7-10 and 21 are cancelled without prejudice.

Claim 12 is rewritten in independent form. The dependencies of claims 13-15 have been changed to be dependent upon claim 12. Claim 17 has been rewritten in independent form and in conformance with U.S. practice. The dependency of claims 18-20 have been corrected so as to be dependent upon claim 17.

The Applicants wish to express their appreciation to the Examiner for agreeing to consider R_c with the scope of the '410 patent with R_a having the formula a or b.

The foregoing amendments overcome the rejection of claims 2-5, 7-10 and 21 under 35 USC 102.

The foregoing amendments further overcome the rejection of claims 17-20 under 35 USC 112.

The remaining rejection is of claims 2-5, 7-10, 12-15 and 17-21 under 35 USC 103 as being unpatentable over Yoshitomi, WO 98/06433, in view of Ono, EP 0 893 437 or Nakamura, EP 0 784 980 or Fujisawa, EP 0 519 354. This ground of rejection is respectfully traversed as applied to the claims after the foregoing amendments.

The cited reference 1 (WO 98/06433) does not describe or suggest that Rho kinase itself is involved in interstitial pneumonia and pulmonary fibrosis. It does not describe or suggest either that a Rho kinase inhibitor is effective for treating interstitial pneumonia and pulmonary fibrosis.

The cited reference 2 (EP 0 893 437) does not described or suggest that Rho kinase itself is involved in interstitial pneumonia and pulmonary fibrosis. It does not described or suggest either that a Rho kinase inhibitor is effective for treating interstitial pneumonia and pulmonary fibrosis. In addition, the enzymes disclosed in this reference and the compounds (pharmaceutical agents) acting on such enzymes are tryptases and tryptase inhibitors, which are completely different from the Rho kinase and Rho kinase inhibitor disclosed in the present invention.

The cited reference 3 (EP 0 784 980) does not describe or suggest that Rho kinase itself is involved in interstitial pneumonia and pulmonary fibrosis. It does not describe or suggest either that a Rho kinase inhibitor is effective for treating interstitial pneumonia and pulmonary fibrosis. In addition, the enzymes disclosed in this reference and the compounds (pharmaceutical agents) acting on such enzymes are collagenases and collagenase accelerators, which are completely different from the Rho kinase and Rho kinase inhibitor disclosed in the present invention.

The cited reference 4 (EP 0 519 354) does not describe or suggest that Rho kinase itself is involved in interstitial pneumonia and pulmonary fibrosis. It does not describe or suggest either that a Rho kinase inhibitor is effective for treating interstitial pneumonia and pulmonary fibrosis. In addition, the enzymes disclosed in this reference and the compounds (pharmaceutical agents) acting on such enzymes are leukocyte elastases and elastase inhibitors, which are completely different from the Rho kinase and Rho kinase inhibitor disclosed in the present invention.

In cited reference 2 and cited reference 4, an enzyme inhibitor is effective for interstitial pneumonia and pulmonary fibrosis, whereas in cited reference 3, an enzyme accelerator is effective for interstitial pneumonia and pulmonary fibrosis. This means different kinds of enzymes exhibit different effects on interstitial pneumonia and pulmonary fibrosis.

From the foregoing, it is concluded that a description relating to a different enzyme cannot be a solid basis for the prediction of the effect of the present invention (i.e., therapeutic effect of Rho kinase inhibitor on interstitial pneumonia and pulmonary fibrosis).

The Examiner is kindly requested to study Experimental Examples 1-4 in the present specification, which clearly demonstrate that the Rho kinase itself is involved in interstitial

pneumonia and fibrosis. The present invention first clarified that a Rho kinase inhibitor is effective for treating interstitial pneumonia and pulmonary fibrosis.

In view of the foregoing, it is believed that each ground of rejection and objection set forth by the Examiner have been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

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ン酸マグネシウムを混合し、直径７ｍｍの杵を用いて、１錠１２０ｍｇの錠剤を製した。

製剤処方例２：カプセル剤

本発明化合物	１０．０ｍｇ
乳糖	７０．０ｍｇ
トウモロコシデンプン	３５．０ｍｇ
ポリビニルピロリドンＫ３０	２．０ｍｇ
タルク	２．７ｍｇ
ステアリン酸マグネシウム	０．３ｍｇ
	１２０．０ｍｇ

本発明化合物、乳糖およびトウモロコシデンプンを混合し、ポリビニルピロリドンＫ３０糊液を用いて練合し、２０メッシュの篩を通して造粒した。５０℃で２時間乾燥した後、２４メッシュの篩を通し、タルクおよびステアリン酸マグネシウムを混合し、硬カプセル（４号）に充填し、１２０ｍｇのカプセル剤を製した。

以下、本発明の医薬の薬理作用を実験例により説明する。

なお、以下の実験例には、Ｒｈｏキナーゼ阻害活性を有する化合物である（＋）－トランス－４－（１－アミノエチル）－１－（４－ピリジルカルバモイル）シクロヘキサン　２ＨＣｌ・１Ｈ$_2$Ｏ（以下、Ｙ－２７６３２と称する）を用いた。Ｙ－２７６３２は各実験において所定の濃度となるよう生理食塩水に溶解・希釈して用いた。

実験例１：ブレオマイシン誘発間質性肺炎（肺線維症）モデルにおけるＲＯＣＫ－ＩＩ遺伝子の発現

（方法）

６週齢（約１５ｇ）の雌のＣ５７ＢＬ／６マウスを一群４匹（ｎ＝４）とし、これに、ブレオマイシンを隔日に５回腹腔内投与して（合計投与量：２００ｍｇ／ｋｇ）、ブレオマイシン誘発間質性肺炎（肺線維症）モデルを作製した。

ブレオマイシン投与開始後７、１４、２１、４０日目の肺におけるＲＯＣＫ－ＩＩ

weighing 120 mg per tablet were prepared.

Formulation Example 2: Capsules

compound of the present invention	10.0	mg
Lactose	70.0	mg
Corn starch	35.0	mg
~~cellulose~~	~~29.7~~	~~mg~~
Polyvinylpyrrolidone K30	2.0	mg
Talc	2.7	mg
Magnesium stearate	0.3	mg
	120.0	mg

The compound of the present invention, lactose and corn starch were mixed, kneaded with polyvinylpyrrolidone K30 paste solution and passed through a 20-mesh sieve for granulation. After drying at 50°C for 2 hours, the granules were passed through a 24-mesh sieve and talc and magnesium stearate were added. The mixture was filled in hard capsules (No. 4) to give capsules weighing 120 mg.

The pharmacological action of the pharmaceutical agent of the present invention is explained in the following by referring to Experimental Examples.

In the following Experimental Examples, a compound having a Rho kinase inhibitory activity: (+)-trans-4-(1-aminoethyl)-1-(4-pyridylcarbamoyl)cyclohexane $2HCl \cdot 1H_2O$ (hereinafter Y-27632) was used. Y-27632 was dissolved and diluted in physiological saline to achieve a predetermined concentration.

Experimental Example 1: Expression of ROCK-II gene in bleomycin-induced interstitial pneumonia (pulmonary fibrosis) model

(Method)

Female C57BL/6 mice (about 15 g, 6-week-old) in 4 mice per group (n=4) were intraperitoneally administered with bleomycin 5 times a day every other day (total dose: 200 mg/kg) to prepare a model with bleomycin-induced interstitial pneumonia (pulmonary